Section (c) - REMARKS

1. The 35 U.S.C. 102(b) Rejection Based on O'Dell

Claims 15-27 are pending in the application. The Examiner has rejected Claims 15, 18, and 19 under 35 U.S.C. 102(b) as being anticipated by U. S. Patent No. 5,356,771 issued on October 18, 1994 to **O'Dell**.

2. Response to the 35 U.S.C. 102(b) Rejection Based on O'Dell

The **O'Dell** patent describes a combined perfusion and oxygenation organ preservation apparatus. The Examiner points to the summary of the O'Dell invention found at column 2, lines 14 through column 3 of the patent for disclosure of a hyperbaric oxygenator which is connected to a biological entity. This summary, however, does not fully capture key operational features of the invention, nor does it highlight the important distinctions between O'Dell and the present invention. The "flexible, gas permeable membrane" 26 described and claimed in the O'Dell patent only allows the passive movement of oxygen molecules from one side of the membrane to the other and the dissolution of the perfusate at near ambient pressure, as the pumping pressure, and thus the perfusion pressure, is restricted to no greater than 20 mmHg. Furthermore, the single membrane oxygenator in O'Dell does not have a sufficiently high surface area to maintain constant oxygenation of the perfusate at high pressures. As noted in the description of Figures 1-3a of the patent, there is a first cycle in O'Dell in which pressure is increased, followed by a negative pressure cycle created as part of the pumping and oxygenation process (see O'Dell, column 6, lines 4-24), thus returning to ambient pressure on the completion of the cycle. As described in Claim 1 of O'Dell, the membrane is "operable upon pressure differentials across the membrane to flex in a first direction so as to displace perfusate from said perfusion compartment through said first passage means into said tissue compartment and in an opposite direction so as

to displace perfusate from the tissue compartment through said second passage means into said perfusion compartment." In contrast, the present invention operates at a pressure of about 2280 mmHg, which pressure is maintained throughout operation.

Thus, O'Dell simply cannot provide the levels of oxygen within the perfusate seen in the present invention. Indeed, because O'Dell's device utilizes a rapidly repeated cycle, the average pressure is ambient and not hyperbaric at all. A close examination of the figures illustrating the membranes 26 in both the pumping chamber 76 and the tissue chamber 74 reveals that as one membrane is depressed, there is a compensatory bulging of the other membrane, which in essence transmits the pressure and therefore does not increase the pressure within the chambers. Applicant has amended Claim 15 to further clarify and emphasize these distinctions between O'Dell and the present invention.

3. **The 35 U.S.C. §102(b) Rejection Based on De Roissart**

The Examiner has rejected Claims 15, 18, 19, 21-27 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 3,772,153 issued on November 13, 1973 to **De Roissart**.

4. **Response to the 35 U.S.C. §102 (b) Rejection Based on De Roissart**

The Examiner states that **De Roissart** discloses an organ preservation apparatus which provides an hyperbaric oxygenated perfusate directly to an organ. Specifically, "Oxygen 25 is supplied to a perfusate container 6 for oxygenating the perfusate. The perfusate is delivered to an organ container 2 via a pump 7. The tube 5 directly connecting the perfusate with the organ 3" (see Office Action, January 29, 2003, page 2-3).

The present invention is significantly simpler in design, function, and efficiency than that described in De Roissart. The present invention does not require a buffer-damper or inert gas. Furthermore, the present invention oxygenates the perfusate with a high surface area oxygenator within a single chamber that holds the biological entity within a sustained pressure environment greater than one atmosphere absolute versus a separate pressurized vessel and pressurized container. This novel configuration takes full advantage of the gas laws to increase the deliverable oxygen significantly higher than that of De Roissart. Indeed, De Roissart makes great efforts in teaching that the high pressure tank 25 is filled with helium containing a small amount of oxygen (see De Roissart, column 4, lines 18-19). De Roissart further states: "Considering the operational features, the gas in the tank 25 may contain volumetrically 99 percent helium and 1 percent oxygen. The pressure regulator 35 is adjusted such that in the conduit 34, and therefore in the vessel 2, there is about 5-10 bars of pressure. The pressure regulator 24 is so adjusted that the pressure in the supply container 6 should be a few bars less than that in the vessel 2" (see *id.*, column 4, lines 56-64). Using the maximum values of 10 bars and 1% oxygen in the mixture, the resultant partial pressure of oxygen is only 0.1 ATA as 1 bar equals 1 atmosphere. The partial pressure of oxygen at sea level is 0.21 ATA. Consequently, De Roissart's invention supplies an amount of oxygen actually less than that at normal sea level and thus is relatively hypobaric from a partial pressure aspect compared to the partial pressure of oxygen in room air.

The current invention will instead result in an oxygen partial pressure of 3.0 ATA under the desired configuration. This is 14.28 times the level maximally achieved by De Roissart. There is a definite distinction between hyperbaric (high pressure gas) and hyperbaric oxygen (high pressure oxygen). Thus, the invention disclosed by De Roissart does not teach the present

invention. There are clearly distinct elements in the respective systems designed to achieve clearly different results.

For example, the physical mechanics of the present invention require an open container since vessel 10 is barometrically pressurized. A closed container would be at risk of collapsing or breaking due to the expected barometric pressure. This novel configuration provides the advantage of retaining the oxygen dissolved into the perfusate by the high surface area oxygenator. De Roissart, having technically four separate pressurized containers and vessels as seen in Figure 1, loses oxygen from the conduits as the perfusate travels from container to vessel. Furthermore, De Roissart's configurations require the elaborate use of a buffer-damper and cumbersome compression and decompression operations of all of the containers and vessels as taught at column 6, lines 4-51.

Additionally, the present invention as claimed utilizes a high pressure pump which is capable of forcing the perfusate into the pressurized vessel as well as to perfuse the tissue of the biological entity. Such perfusion requires a pump capable of producing a high enough fluid pressure to equal that of the barometric pressure of at least 29.4 pounds per square inch in the vessel plus the pressure needed in order to perfuse the biological entity in the preferred embodiment. De Roissart fails to anticipate such a requirement and merely mentions "a pump" in both the description of the invention and the claims without any restriction or requirement parameters.

Moreover, the present invention teaches a closed perfusion system in the preferred embodiment, which takes advantage of the relative negative pressure created by the barometric pressure within the vessel and that of the room ambient pressure. The result of this barometric pressure gradient is the active pulling of the perfusate from the compressed vessel, thus

facilitating the circulation of the perfusate. De Roissart fails to anticipate such a configuration as the perfusate pressure is kept essentially the same throughout the system. The novel aspects of the current invention's preferred embodiment is that such a configuration mimics the venous pressure differential physiology seen in natural vasculature. In doing so, the tissue is not engorged as seen in the prior art and cellular damage is minimized.

The current invention teaches "access to the perfusate can be obtained by an access port 52 on the perfusate container or along the fluid delivery tubes similar to that seen with intravenous tubing" (Application, page 16, line 31 - page 17, line 1). De Roissart fails to anticipate such a configuration as the system is kept at a constant perfusate pressure throughout. The closest element is "a regulating valve 43" mentioned in column 4, line 36, which only allows for the replenishment of the nutrient fluid from a flask 41 subjected to the same environmental pressure as the pressurized container 6 (see De Roissart, column 4, lines 29-31). This separately pressurized area that De Roissart even fails to numerically identify, adds to the cumbersome nature of the invention. If the flask 41 becomes empty, the whole system would require depressurization which, as mentioned earlier, is very complicated. Similarly, any access port inserted along the conduits in De Roissart's invention would require a pressurized access port, depressurization, or a means capable of overcoming the perfusate pressure within the conduit in order to use it. The physical difference in the current invention is significant and novel in that the access port is readily available on the negative pressure aspect of the invention's circuit similar to that seen in inserting an intravenous line into a person or animal. This allows means to those familiar with the art to quickly use the access port without difficulty.

With respect to the addition of drugs to the system, De Roissart focuses only on low temperature, perfusion, the hyperbaric (and specifically not a hyperbaric oxygen) environment,

and the removal and prevention of gaseous embolisms. De Roissart does not provide means for treating or studying drugs or pharmaceutical agents' effects on the biological entity nor does it suggest this possibility.

Furthermore, the present invention permits waste products to be removed from the system, thus prolonging the function of the invention and the viability of the biological entity. In addition, the perfusate can be analyzed or tested including, but not limited to biochemical, microbiological, enzymatic, electrolyte, or nutritional analysis or testing. Again, this capability would be impossible by De Roissart without the complicated decompression of the system as a whole.

Similarly, although De Roissart teaches the replenishment of nutrient fluid to the system, it does so only to replace the fluid that is lost in the constant level tank 15 during the process of the system compression and decompression. Again, once the flask is empty in De Roissart's invention, it can only be replaced by decompressing the system. The novel use of the perfusate in the present invention allows the dilution of waste products toxic to the biological entity, thus promoting the prolongation of the support time available for the biological entity. Such a function, and the requisite structures, are neither supported or suggested by the De Roissart disclosure.

5. **The 35 U.S.C. §103 (a) Rejection Based on De Roissart in view of Hassanein**

The Examiner has rejected Claims 16, 17, and 20 under 35 U.S.C. §103 (a) as being unpatentable over U.S. Patent No. 3,772,153 issued on November 13, 1973 to **De Roissart** in view of U.S. Patent No. 6,100,082 issued on August 8, 2000 to **Hassanein**.

6. **Response to the 35 U.S.C. §103(a) Rejection Based on De Roissart in view of Hassanein**

De Roissart uses a complicated system to preserve the organ under hyperbaric conditions, but not hyperbaric oxygen conditions. The system interconnects four separately pressurized containers and uses a mixture of an inert gas (preferably helium) and no more than 1% oxygen to both pressurize the system and to oxygenate the perfusate via agitation of the perfusate. There are many disadvantages in the De Roissart system which are overcome by the present invention. First, the present invention is a single pressurized unit, thus simpler in design and control. Second, De Roissart takes considerable time explaining how to prevent gas embolism from blocking the organ's vessels. If this were to occur, the organ would have a high risk of dying. An embolus may occur in the De Roissart system due to the inert gas coming out of solution and forming bubbles within the blood vessels when the system is depressurized. This is similar to bubbles coming out of solution when a soda is opened. The present invention is pressurized with about 100% oxygen that is metabolically active unlike any inert gas and does not come out of solution when the system is depressurized. Third, the De Roissart system relies on oxygenation of the perfusate in a nutrient fluid container. The oxygenation occurs at the surface between the perfusate and the pressurized gas mixture, thus also dissolves the inert gas as well. This follows standard gas diffusion laws. Even though De Roissart has an agitator, this is a very inefficient means of driving the gas into solution because of the relatively small surface area between the gas and fluid.

The present invention overcomes this obstacle by actively using a high surface area oxygenator within the pressurized system. This dramatically increases the relative surface area between the fluid and oxygen used in the present invention, thus quickly oxygenating the

perfusate. The present invention, preferably using a minimum of 3.0 atmospheres absolute, makes the oxygen readily available to the biological entity at a partial pressure that is 14.28 times the levels maximally achieved by De Roissart. This in turn decreases the likelihood of reperfusion injury. The present invention also can supply sufficient oxygen to the biological entity to continue normal metabolism at normal body temperature, not possible with the De Roissart system.

Hassanein also uses a complicated system to preserve the organ under normobaric conditions but also normothermic; that is at ambient room pressure and the system at 37 degrees centigrade. Hassanein focuses heavily on preserving the heart, but mentions adaptation for other specific solid organs. It also focuses on the use of blood as the primary perfusate. With a designated gas mixture of 95% oxygen and 5% carbon dioxide, at best conditions, the oxygen content obtainable within the Hassanein invention is that of blood at one atmosphere. It would be significantly lower for most other fluids. Hassanein strictly uses hot water exchange for keeping the temperature at 37 degrees centigrade and discounts any hypothermic storage of organs. The present invention is not limited to such parameters. As Hassanein's invention is at ambient pressure, the oxygen levels achieved in the present invention are much higher.

As described in the present invention, the biological entity includes, but is not limited to, kidney, heart, lungs, liver, spleen, bone, brain, or any other such organ, extremities or parts thereof, tissues or bioengineered organs or tissues. The present invention does allow the surgeon or investigator to have a range of temperatures to store the biological entity, thus finding an optimal temperature. Finally, as the present invention does not use blood as Hassanein's preferred embodiment, there is not the risk of incompatibility or infectious products within the blood with which to contend.

Thus, De Roissart and Hassanein do not contain any justification or teaching toward their combination, particularly toward achieving the distinct functionality of the present invention. The Examiner states that "It would have been obvious to one skilled in the art to provide the means for adding chemicals and measuring and filter of the Hassanein device to the De Roissart device in view of the known advantages and benefits disclosed in Hassanein" (see Office Action, January 29, 2003, page 3). The fact that both references teach means of organ preservation is not sufficient to selectively add parts of one reference to another reference in order to meet Applicant's novel claimed configuration. In fact, the references of De Roissart and Hassanein teach away from the suggested combination. De Roissart emphasizes the preservation of living tissue using a low temperature by means of refrigerating the organ vessel and the perfusate container and a hyperbaric environment up to 10 bars (ATA). De Roissart teaches the oxygen content to be 1% in order to avoid the "toxic effect of excess oxygen in the tissues, such excess being inevitable when pure oxygen or a high percentage oxygen mixture was being used as the hyperbaric agent or for the oxygenation of the perfusion liquid" (see De Roissart, column 1, lines 58-63).

Hassanein emphasizes the preservation of the donor organ by implementing a method of continuous sanguinous perfusion and at normothermic temperatures by means of a water heater providing warmed water through a water circuit to heat the blood in the preferred embodiment. The gas used to oxygenate the blood in Hassanein is a mixture of 95% oxygen and 5% carbon dioxide in a normobaric or ambient room pressure. The references essentially teach nearly opposite methods of preserving organs. Indeed, the references teach away from each other via mutually exclusive paths to reach different solutions to a similar problem. Thus, since they teach away from each other, it would not be logical to combine them.

Because of the divergence of methods used by De Roissart and Hassanein, it would be necessary to make modifications, not taught in the prior art, in order to combine the references in the manner suggested. For example, adding De Roissart's hyperbaric environment to the organ and perfusate containers in Hassanein's device would significantly alter the fluid pressures and dynamic flow so important to Hassanein's device mentioned in the careful monitoring of the aortic, coronary, and afterload pressures with the pressure catheters. Means of counteracting the changes resulting from combination with De Roissart to obtain the same flow parameters would make Hassanein's invention even more complicated and cumbersome.

7. Summary

The results achieved by the present invention have significant synergism over the respective results of the individual references. The results of the present invention are superior to either that described by O'Dell, De Roissart, or Hassanein in that the amount of oxygen driven into the perfusate by means of a high surface area device under pressure far exceeds that of any of the referenced patents. Furthermore, because of the pressure differentials established at the biological entity (high fluid pressure of the perfusate at the entity's arterial vasculature and low pressure at the venous side), a system is provided that is closer to natural physiology than any of the referenced patents. The present system also allows for a temperature range that can be optimized and tailored to the preservation of a variety of biological entities depending on the reason for preservation; that is transplantation, biomedical studies, repair, etc.

The present invention is able to oxygenate the biological entity far better than that seen by any of the referenced patents. In doing so, it also reduces the damage done in a hypoxic state and consequent reperfusion injury to the biological entity significantly better than the prior art.

CONCLUSION

Thus, Applicant has addressed each of the Examiner's rejections by modifying the claims to more fully distinguish the present invention over the prior art and setting forth the novel features of the present invention which clearly distinguish it from the cited references. It is respectfully requested that upon reconsideration the Examiner issue a notice of allowance. Should the Examiner feel that the prosecution of the above-identified application may be materially advanced by a telephone call; the Examiner is hereby requested to call the undersigned.

Respectfully submitted,
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